

IN THE SPECIFICATION:

Please replace the paragraph starting on page 25, line 13, and ending on line 18 with the following paragraph.

A fiber protein of adenovirus 16 preferably comprises at least part of the sequence given in ~~FIG. 7~~ FIGS. 7A-C. However, within the scope of the present invention, other sequences may be used, for instance, obtained through using codon degeneracy. Alternatively, a fiber sequence may comprise amino-acid substitutions or insertions or deletions compared to the sequence depicted in ~~FIG. 7~~ FIGS. 7A-C, as long as the desired tissue tropism determining property is not significantly altered. Amino-acid substitutions may be within the same polarity group or without.

Please replace the section entitled BRIEF DESCRIPTION OF THE DRAWINGS with the following section.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

FIG. 1: Schematic drawing of the pBr/Ad.Bam-rITR construct.

FIG. 2: Schematic drawing of the strategy used to delete the fiber gene from the pBr/Ad.Bam-rITR construct, using primers NY-UP (SEQ ID NO: 36) and NY-DOWN (SEQ ID NO: 37).

FIG. 3: Schematic drawing of construct pBr/Ad.BamRDfib.

FIG. 4: Nucleotide sequence of chimeric fiber Ad5/fib16, SEQ ID NO: 32.

FIG. 5: Schematic drawing of the construct pClipsal-Luc.

FIG. 6: Schematic drawing of the method to generate chimaeric adenoviruses using three overlapping fragments. Early (E) and late regions (L) are indicated. L5 is the fiber coding sequence.

FIGS. 7A, 7B & 7C: Sequences including the gene encoding adenovirus 16 fiber protein as published in GenBank with nucleotide sequence SEQ ID NO: 33 and amino acid sequence SEQ ID NO: 35; and sequences including a gene encoding a fiber from an adenovirus 16 variant as isolated in the present invention with nucleotide sequence SEQ ID NO: 38 and amino acid sequence SEQ ID NO: 34, wherein the sequences of the fiber protein are from the NdeI-site. FIG. 7A FIGS. 7A & 7B nucleotide sequence comparisons of SEQ ID NO: 33 and SEQ ID NO: 38. FIG. 7B FIG. 7C amino-acid comparisons of SEQ ID NO: 35 and SEQ ID NO: 34.

FIG. 8: Infection of synoviocytes using different amounts of virus particles per cell (MOI) and two different adenoviruses: Ad5=Ad5.Clip.Luc; Ad5/16= Ad5.Luc-fib16. Luciferase transgene expression, 48 hours after a 2 hours infection procedure is depicted as relative light units (=RLU) per microgram whole cell lysate. Error bars represent standard error of the mean (SEM).

FIG. 9: Infection of synoviocytes using different concentrations of cells. Luciferase transgene expression, 48 hours after a 2 hours infection procedure is depicted as relative light units (=RLU) per microgram total protein. Error bars represent SEM. The actual MOI differed between the cell concentrations and ranged from 20,000 virus particles per cell (cell density 12,500) to 2,500 virus particles per cell (cell density 100,000).

FIG. 10: Infection of synoviocytes using different virus exposure periods. Luciferase transgene expression, 48 hours after either a 2 hours or a 20 hours virus exposure is depicted as relative light units (=RLU) per microgram protein. Error bars represent standard deviations.

FIG. 11: Synoviocytes were incubated with IG.Ad.CMV.TK or IG.Ad.mlp-I.TK. Cells were cultured with or without GCV.

FIG. 12: Bystander killing was assessed in cultures containing both TK-infected and non-TK-infected synoviocytes in a proportion 0/100, 50/50, 25/75 and 0/100. Cells were cultured with or without GCV.

FIGS. 13 A & B: X-gal expression in synovial tissue 3 days after intra-articular injection of IG.Ad.CMV.lacZ in the knee. 13A: macroscopy. 13B: direct LacZ staining of synovial tissue counterstained with Mayers Hamalanlosung.

FIG. 14 is a graph comparing infection of Ad5.luc and Ad5.fib16.luc on RA synoviocytes.

FIG. 15 is a graph depicting the percentage of lacZ positive cells with Ad5.lacZ and Ad5.fib16.lacZ in RA synoviocytes.

FIG. 16 A & 16B are graphs depicting the infection efficiency of Ad5.GFP and Ad5.fib16.GFP in RA synoviocytes and the respective luciferase counts respectively.

FIG. 17 is a graph depicting the infectivity of chimeric adenoviruses on RA synoviocytes.

FIG. 18A is a graph depicting the percentage of infected cells with three B-type fiber-modified viruses on RA synoviocytes.

FIG. 18B is a graph depicting GFP production with three B-type fiber-modified viruses on RA synoviocytes.

FIG. 19 is a graph depicting the comparison of three B-type fiber-modified adenovirus for infectivity on RA synoviocytes.

FIG. 20 is a graph depicting the comparison of infectivity Ad5.lacZ vs. Ad5.fib16.lac6 in RA synoviocytes fro six patients.

IN THE DRAWINGS:

Please delete the drawing figures and replace them with the attached replacement drawing figures.

The attached drawing sheets include FIGS. 1-20. These sheets, which include FIGS. 1-20, replace the original sheets including FIGS. 1-20.

Specifically, FIGS. 1, 3, and 5 have been reduced in size to comply with the requested margin sizes.

FIG. 2 has been revised to be more visible and reproducible.

FIG. 4 has been revised to remove the figure description and rotated on the page to be more uniform and comply with the requested margin sizes.

FIG. 6 has been revised by removing the boxed heading and sized to comply with the requested margin sizes.

FIG. 7A has been revised by rotating and spacing the text on multiple sheets, thus, resulting in FIGS. 7A and 7B.

Revised FIG. 7C shows the text from the previous FIG. 7B and has been revised by rotating and sizing the text to the requested margin sizes.

FIGS. 8-10 have been revised by rotating and resizing the figure to be uniform and within the requested margin sizes.

FIG. 11 has been revised to remove the border and sized to comply with the requested margin sizes.

FIG. 12 has been sized to comply with the requested margin sizes.

FIGS. 13A and 13B are resubmitted as color photographs that comply with the requested margin sizes.

FIGS. 14-20 have been revised by removing the figure description, rotating the figure, and resizing the figure to be uniform and fit within the requested margin sizes.